REMARKS

All claims were rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. In the previous filed response, applicants referred to page 10 of the specification. This was a typographical error in that the support appears on page 12. In light of this correction, it is respectfully submitted that the written description requirement has been satisfied and withdrawal of this rejection is respectfully solicited.

All claims are rejected under 35 USC § 103 over Veech and Vinnars. This rejection is respectfully traversed.

Veech teaches a parenteral nutritional solution which comprises water having dissolved therein (a) at least one of the 20 metabolizable nitrogen compounds set forth in Table 5, (b) at least one carboxylic anion selected from a group of six materials, one of which is α-ketoglutarate, and (c) at least one cation selected from a group of five materials, one of which is ammonium. The reference thus teaches a vast number of combinations and permutations possible including, *inter alia*, the combination of α-ketoglutarate and ammonium. However, whenever this (or any other) combination is present, the two entities are always in the same composition. The Office Action acknowledges there is no teaching or suggestion set forth which would motivate one skilled in the art to separate them into individual compositions. Ammonium is a cation and to separate it from the anion makes little, if any, sense.

Vinnars teaches the addition of α-ketoglutarate, alone or in combination with conventional amino acids solutions, to a parenteral nutritional program. No reference to the use of an ammonium material in this reference has been found. Clearly this reference does not provide any suggestion for administering α-ketoglutarate and ammonium in separate compositions.

The Office Action avers that a person skilled in the art would have been motivated to use two separate compositions because both α-ketoglutarate and ammonium are known to be useful in the same method. The Office Action continues with the observation that "combining two agents which are known to be useful...individually into a single composition useful for the very same purpose is prima facie obvious." It is respectfully pointed out that these observations are not pertinent to any of the claims pending in this application. The applicants are not combining two agents into a single composition, but quite to the contrary , they are providing two separate compositions. Moreover, the art of record does not teach or suggest and ammonium was "known to be useful...individually...." As the Office Action points out, Veech includes a composition which contains both α-ketoglutarate and ammonium, but there is no apparent reason to separate these into separate compositions. Indeed, administering two compositions when one will do is counterintuitive.

The present invention provides a specific dosage unit comprising two separate compositions, one containing α-ketoglutarate and/or α-ketoglutarate acid and the other containing ammonium. The provision of these agents in separate pharmaceutical compositions is called for by the specific mmanner of their administration. The efficacy of the method of the present invention and the unobvious superior usefulness of the combination of the compositions is not disclosed or suggested by Veech or Vinnars, whether considered alone or in combination. This is an additional reason for allowance of this case.

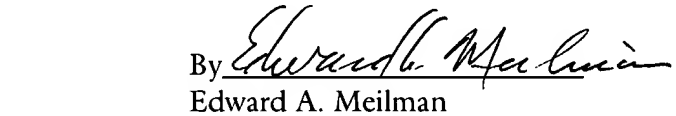
The Office Action states that applicants have failed to set forth evidence substantiating the unexpected benefits. In response, applicants respectfully draw the Examiner's attention to the data set forth in the application, particularly when viewed in light of the articles submitted with the last Amendment. The paper by Wiren (2002) describes a study to evaluate the feasibility of using α-ketoglutarate enrichment in enteral feeding and the effect on protein metabolism after major surgery. The authors concluded that enrichment of a whole protein-based formula with α-ketoglutarate did not improve

protein metabolism or decrease muscle catabolism after major abdominal surgery. See e.g., the summary on page 725 and the concluding paragraph in the paper. The findings of the study were sufficiently important to elicit an editorial opinion. Note that the concluding sentence by Dr. Cynober in that opinion states that based on both the Wiren study and the available literature, there is no rational for providing an α-ketoglutarate enriched enteral diet in post-operative patients. These documents, which teach against employment of α-ketoglutarate alone, would clearly dissuade one skilled in the art from presenting α-ketoglutarate and ammonium in separate preparations, particularly where Veech can be argued to indicate that their provision in the same composition can give positive results.

In light of all of the foregoing considerations, it is respectfully submitted that the rejection should be withdrawn and the application allowed.

Dated: October 31, 2003

Respectfully submitted,

By 

Edward A. Meilman
Registration No.: 24,735
DICKSTEIN SHAPIRO MORIN & OSHINSKY LLP
1177 Avenue of the Americas
41st Floor
New York, New York 10036-2714
(212) 835-1400
Attorney for Applicant(s)

ACIDIFYING AGENTS 40:04

Ammonium Chloride

NH_4Cl

Chemistry and Stability

■ **Chemistry**

Ammonium chloride is an acid-forming salt. Ammonium chloride occurs as colorless crystals or a white, fine or coarse, crystalline powder. The drug has a cool, saline taste and is somewhat hygroscopic. Ammonium chloride is freely soluble in water (1:3) and sparingly soluble in alcohol (1:100). Aqueous solutions of ammonium chloride have a salty taste which can be masked by raspberry, cherry, or other acidic syrups.

Each gram of ammonium chloride contains 18.7 mEq each of ammonium and chloride ions. The 26.75% concentrate for injection contains ammonium chloride 5.35 g/20 mL or 5 mEq each of ammonium and chloride ions per mL; the 26.75% concentrate for injection has a calculated osmolarity of 10.018 mOsm/mL. Following dilution of 20 mL of the 26.75% concentrate for injection in 500 mL of 0.9% sodium chloride injection, the resultant dilution contains 200 mEq of ammonium and 354 mEq of chloride ions per liter.

Ammonium chloride concentrate for injection (26.75%) contains disodium edetate as a stabilizer. Hydrochloric acid may be added during the manufacture of the 26.75% concentrate for injection to adjust the pH to 5.

■ **Stability**

Ammonium chloride concentrate for injection should be stored at a temperature of 40°C or less; freezing should be avoided. Concentrated solutions of ammonium chloride may crystallize when exposed to low temperatures. If crystallization occurs, the concentrate for injection should be warmed to room temperature in a water bath prior to use.

Ammonium chloride is incompatible with alkalies and their carbonates and with lead and silver salts. Explosive mixtures may result if ammonium chloride is compounded with potassium chlorate or other strong oxidizing agents.

Pharmacology

The acid-forming properties of ammonium chloride result from dissociation of the salt to an ammonium cation and a chloride anion. In patients with normal hepatic function, the ammonium cation is converted to urea by the liver and a hydrogen cation is released which reacts with a bicarbonate ion to form water and carbon dioxide. The chloride anion combines with fixed bases in the extracellular fluid, thereby reducing the alkaline reserve of the body. The net result is the displacement of bicarbonate ions by chloride anions:

$$2\,NH_4^+ + 2\,Cl^- + 2\,HCO_3^- \rightarrow CO(NH_2)_2 + CO_2 + 3\,H_2O + 2\,Cl^-$$

The displacement of bicarbonate by chloride alters the bicarbonate:carbonic acid ratio of the body and acidosis results.

The increased chloride concentration in the extracellular fluid produces an increased load to the renal tubules and appreciable amounts of chloride anions escape reabsorption. These anions are excreted along with cations and water. Sodium is the principal cation excreted; however, potassium excretion may also be increased to some degree. By increasing the excretion of both extracellular electrolytes and water, ammonium chloride causes a net loss of extracellular fluid and promotes the mobilization of edema fluid. A diuretic response occurs in both normal and edematous patients. The diuretic effect of ammonium chloride is generally overridden by compensatory renal effects within 3 days of continuous therapy with the drug. (See Pharmacokinetics.)

Although the safety and efficacy of ammonium chloride as an expectorant have not been established, it has been suggested that the drug may act as an expectorant by reflex stimulation of bronchial mucous glands resulting from irritation of gastric mucosa following oral administration of the drug.

Pharmacokinetics

Following oral administration, ammonium chloride is rapidly absorbed from the GI tract, complete absorption occurring within 3–6 hours. The drug is metabolized in the liver to form urea and hydrochloric acid. (See Pharmacology.) If ammonium chloride is administered for only 3 or 4 days at a time, it usually produces a mild asymptomatic acidosis. However, if it is given continuously, particularly to patients with renal impairment, it may cause severe metabolic acidosis. The kidney usually compensates for sodium loss by elaborating ammonia through the deamination of amino acids, secreting hydrogen cations in exchange for sodium cations, and thereby excreting chloride anions in combination with ammonium cations. This compensatory effect reaches its peak within about 3 days, at which time ammonium chloride will be eliminated by the kidneys as rapidly as it is ingested. Once this balance occurs, the drug is no longer effective as a diuretic.

Uses

Ammonium chloride is used as a systemic acidifier in patients with metabolic alkalosis resulting from chloride loss following vomiting, gastric suction, gastric fistula drainage, and pyloric stenosis. Ammonium chloride may also be useful in the treatment of diuretic-induced chloride depletion. A solution containing isotonic or hypotonic sodium chloride with potassium chloride is usually more effective than ammonium chloride in hypokalemic patients. Ammonium chloride may also be useful in treating alkalosis resulting from excessive use of alkalinizing drugs.

Ammonium chloride has been used in a variety of conditions to induce incipient acidosis for the purpose of promoting diuresis, particularly in edematous conditions associated with hypochloremia. Ammonium chloride has limited value as a diuretic when used alone because of its limited period of effectiveness, but the drug may be useful alone or in combination with a xanthine diuretic (e.g., caffeine, pamabrom) for *short-term* therapy to relieve temporary water-weight gain, edema, bloating, and/or full feeling associated with premenstrual and menstrual periods. Ammonium chloride has also been used for its diuretic effect in Ménière's syndrome.

Ammonium chloride has also been used to increase the solubility of calcium and phosphate ions in the management of patients with phosphatic calculi in the urinary tract and to increase calcium inization in alkalotic tetany. The drug has also been used in the treatment of lead poisoning to solubilize calcium and facilitate excretion of the lead-calcium complex; but more effective treatments (e.g., edetate calcium disodium, dimercaprol) are currently available. Ammonium chloride has also been used in the treatment of bromism.

Ammonium chloride has also been used as an adjunct in the treatment of urinary tract infections when a low urinary pH is desired. During therapy with methenamine salts, ammonium chloride is used to acidify the urine to ensure the dissociation of formaldehyde from methenamine. Some clinicians, however, discourage the use of the drug in this manner because of the occurrence of concurrent systemic acidosis; acidosis can be avoided by administering other acidifying agents such as ascorbic acid. Ammonium chloride has also been used as an expectorant, usually in combination with other expectorants and cough mixtures.

Cautions

■ **GI Effects**

Following oral administration, ammonium chloride, especially in large doses, is irritating to the gastric mucosa and may cause gastric distress, anorexia, nausea, vomiting, and thirst. Administration of enteric-coated ammonium chloride tablets may minimize adverse GI effects; however, absorption from this dosage form is unpredictable. Patients using ammonium chloride for *self-medication* should be warned that the drug may cause nausea, vomiting, and GI distress.

■ **Metabolic and Electrolyte Effects**

Large doses of ammonium chloride may cause metabolic acidosis secondary to hyperchloremia, especially in patients with impaired renal function. Acidosis or electrolyte loss resulting from ammonium chloride therapy may be treated with IV sodium bicarbonate or sodium lactate. Potassium depletion has been reported during ammonium chloride therapy and potassium gluconate may be administered orally if hypokalemia results.

■ **Local Effects**

Adverse local effects, including pain and irritation, have occurred at the site of injection or along the venous route following rapid IV administration of ammonium chloride. These local effects may be decreased by administering the drug slowly during IV infusion.

■ **Other Adverse Effects**

Other adverse effects of excessive ammonium chloride dosage include rash, headache, hyperventilation, bradycardia, progressive drowsiness, mental confusion, and phases of excitement alternating with coma. Calcium-deficient tetany, hyperglycemia, glycosuria, twitching, hyperreflexia, and EEG abnormalities have also been reported. Most of these adverse effects are secondary to ammonia toxicity resulting from inability of the liver to convert the ammonium ion to urea. Because rapid IV injection may increase the likelihood of ammonia toxicity, IV infusions of ammonium chloride should be administered slowly to permit metabolism of ammonium ions by the liver.

■ **Precautions and Contraindications**

Patients receiving ammonium chloride should be closely monitored for signs and symptoms of ammonia toxicity such as pallor, sweating, irregular

breathing, vomiting, bradycardia, cardiac arrhythmias, local or generalized twitching, asterixis, tonic seizures, and coma.

Prior to IV infusion of ammonium chloride and during therapy, the carbon dioxide combining power of the patient's serum should be monitored to avoid serious acidosis.

Ammonium chloride should be administered with caution to patients with pulmonary insufficiency or cardiac edema. The drug should not be used in patients with primary respiratory acidosis and high total carbon dioxide and buffer base.

Sustained correction of hypochloremia cannot be achieved by administering ammonium chloride alone in patients with secondary metabolic alkalosis resulting from intracellular potassium depletion; concomitant administration of potassium chloride is necessary in such patients.

In patients with severe renal dysfunction, ammonium chloride should not be used alone when metabolic alkalosis secondary to vomiting of hydrochloric acid is accompanied by substantial sodium loss. In such patients, sodium chloride repletion, alone or in combination with ammonium chloride, may be necessary to correct both sodium and chloride depletion. In addition, ammonium chloride should not be used for *self-medication* in patients with renal disease.

Ammonium chloride should not be administered to patients with severe hepatic dysfunction, since ammonia toxicity may occur in these patients. In addition, ammonium chloride should not be used for *self-medication* in patients with hepatic disease.

■ Pediatric Precautions

Safety and efficacy of ammonium chloride concentrate for injection in children have not been established.

■ Pregnancy

Animal reproduction studies have not been performed with ammonium chloride. It is not known whether ammonium chloride can cause fetal harm when administered to pregnant women. Ammonium chloride should be used during pregnancy only when clearly needed.

Dosage and Administration

■ Administration

As an acidifying agent, ammonium chloride is administered orally or by slow IV infusion. Ammonium chloride is administered orally as a diuretic. Solutions of the drug should not be administered subcutaneously, intraperitoneally, or rectally. The 26.75% concentrate for injection *must* be diluted in 0.9% sodium chloride injection prior to administration. A dilute solution may be prepared by adding 100 or 200 mEq of ammonium chloride (20 or 40 mL of the 26.75% injection) to 500 or 1000 mL of 0.9% sodium chloride injection. For IV infusion, the dilute solution should be administered at a rate not exceeding 5 mL/minute in adults.

■ Dosage

The usual adult oral dosage of ammonium chloride is 4–12 g daily administered in divided doses every 4–6 hours. The usual oral acidifying dose for children is 75 mg/kg daily given in 4 divided doses. Adverse GI effects may be minimized by administering the drug after meals.

For the treatment of metabolic alkalosis, ammonium chloride is usually administered by IV infusion. Dosage of the drug depends on the severity of the alkalosis and the tolerance of the patient. Dosage may be determined on the basis of the patient's carbon dioxide combining power. Each gram of ammonium chloride will reduce the carbon dioxide combining power of a 70-kg adult by about 1.1 volume %, or 16 mg/kg will lower the carbon dioxide combining power by 1 volume %. Alternatively, in the absence of edema or hyponatremia, dosage may be calculated on the basis of chloride deficit by the following formula:

$$\textit{mEq of chloride ion (as ammonium chloride)} = \textit{chloride deficit (in mEq/L)} \times 0.2 \times \textit{body weight (in kg)}$$

Approximately one-half the calculated volume of ammonium chloride solution should be administered; the carbon dioxide combining power should be rechecked and necessity for further treatment determined. IV solutions of ammonium chloride should be administered very slowly to avoid ammonia toxicity. (See Cautions: Other Adverse Effects.)

For use as a diuretic, the usual adult oral dosage of ammonium chloride is 4–12 g daily administered in divided doses every 4–6 hours. The drug is most effective as a diuretic when given for 3 or 4 days followed by a rest period of a few days after which therapy is resumed.

For the relief of temporary water-weight gain, edema, bloating, and/or full feeling associated with premenstrual and menstrual periods in adults, the usual oral dosage of ammonium chloride for *self-medication* in adults is 1 g 3 times daily for no longer than 6 days.

For the treatment of Ménière's syndrome, the oral dosage of ammonium chloride is 3 g given 3 times daily with meals for 3 days. The drug is then omitted for 2 days and the cycle is repeated indefinitely.

For use in the treatment of premenstrual edema, 3 g of ammonium chloride may be given daily in divided doses for 4–5 days prior to menstruation.

Preparations

Ammonium Chloride

Oral		
Tablets, delayed-release (enteric-coated)	500 mg*	**Ammonium Chloride Enseals®, Lilly**
Parenteral		
Concentrate for injection	26.75% (5 mEq of NH_4^+ and Cl^- per mL)	**Ammonium Chloride Injection, Abbott**

*available by nonproprietary name

ALKALINIZING AGENTS 40:08

Sodium Bicarbonate

Baking Soda
Sodium Acid Carbonate
Sodium Hydrogen Carbonate
$NaHCO_3$

Chemistry and Stability

■ Chemistry

Sodium bicarbonate is an alkalinizing agent. Sodium bicarbonate occurs as a white, crystalline powder which has a saline and slightly alkaline taste. The drug is soluble in water and insoluble in alcohol. Aqueous solutions of sodium bicarbonate, when freshly prepared, are alkaline to litmus; alkalinity increases as the solutions stand, are agitated, or are heated. Each 84 mg or 1 g of sodium bicarbonate contains 1 or about 12 mEq, respectively, each of sodium and bicarbonate ions.

Sodium bicarbonate injections are sterile solutions of the drug in water for injection. Carbon dioxide may be added during the manufacture of the injection to adjust the pH to 7–8.5. An 8.4% solution contains 1 mEq each of sodium and bicarbonate ions per mL and has a calculated osmolarity of 2000 mOsm/L. A 7.5% solution contains 0.892 mEq/mL each of sodium and bicarbonate ions and has a calculated osmolarity of 1786 mOsm/L. A 5% solution contains 0.595 mEq each of sodium and bicarbonate ions per mL and has a calculated osmolarity of 1190–1203 mOsm/L. A 4.2% solution contains 0.5 mEq each of sodium and bicarbonate ions per mL and has a calculated osmolarity of 1000 mOsm/L. Sodium bicarbonate is also available as a 4% small volume parenteral additive solution (Neut®) which provides 2.4 mEq each of sodium and bicarbonate ions per 5 mL and is used to increase the pH of acidic infusion solutions.

A 1.5% solution of sodium bicarbonate is isotonic. A 1.5% sodium bicarbonate solution can be prepared by diluting each mL of an 8.4, 7.5, or 4.2% solution of the drug with 4.6, 4, or 1.8 mL of sterile water for injection, respectively.

■ Stability

Sodium bicarbonate tablets and effervescent tablets should be stored in tightly closed containers at a temperature less than 40°C, preferably between 15–30°C. Sodium bicarbonate injection should be stored at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided.

Sodium bicarbonate is stable in dry air, but slowly decomposes into sodium carbonate, carbon dioxide, and water in moist air. When heated, sodium bicarbonate loses water and carbon dioxide and is converted into sodium carbonate. Solutions of sodium carbonate are much more alkaline than sodium bicarbonate; since sodium carbonate may be formed when the dry salt or its solutions are sterilized with heat, the pH of heat-sterilized solutions or of solutions prepared from heat-sterilized powder should be determined prior to use.